CLINICAL TRIAL OF IMIPENEM/CILASTATIN IN SEVERELY BURNED AND INFECTED PATIENTS

Gary R. Culbertson, M.D., Albert T. McManus, PH.D., Patrick A. Conarro, M.D., William F. McManus, M.D., F.A.C.S., Arthur D. Mason, Jr., M.D., *and* Basil A. Pruitt, Jr., M.D., F.A.C.S., *San Antonio, Texas*

Imipenem/cilastatin was examined for safety and efficacy in a population of 20 seriously burned patients with acute bacterial infections. The study was made up of 18 males and two females with an average age of 38 years and average burn size of 52 per cent of the total body surface area. Inhalation injury was present in 14 patients. The infections treated included 16 pulmonary, two urinary tract, one wound and one bacteremia. Treatment was clinically successful in 13 patients; five patients had no improvement and the clinical response could not be determined in two in whom multisystem organ failure preceded the treated infection. All of the clinical failures were in the pulmonary infection group. No serious toxicity or side effects were noted. No patient died while receiving the drug or as a consequence of known failure of the drug. Microbiologic success was noted in 12. Resistant organisms developed in eight of whom five were in the clinical failure group. Pseudomonas aeruginosa resistant to imipenem/cilastatin was isolated from seven patients and occurred at an average of 3.6 days after treatment was begun.

INFECTION remains the most common cause of morbidity and mortality in severely burned patients (1). Such an infection is a manifestation of injury related immunosuppression and failure of treatment often resulting from the development of microbial resista

Opportunistic organisms causing infections in burned patients are frequently hospital acquired and may be resistant to multiple antibiotics. The combination of host susceptibility and the possible presence of resistant organisms make the infected burn patient a chemotherapeutic challenge (2, 3). The continuing accumulation of antibiotic resistant organisms in the clinical environment mandates evaluation of the effectiveness and a safety of newly developed antibiotics.

We have examined the effectiveness of imipenem/cilastatin, a novel thienamycin antibiotic, in a group of patients with burns and serious infections. Imipenem/cilastatin is a combination of imipenem, the N-formimidoyl monohydrate derivative of thienamycin, and cilastatin, the sodium salt of a derivatized heptenoic acid which inhibits renal dihydropeptidase (4, 5). Cilastatin increases the renal clearance of imipenem above the glomerular filtration rate, acting in a competitive and freely reversible manner to decrease renal beta-lactam hydrolysis, reduce nephrotoxicity (as seen in animals) and increase the bioavailability of the urinary tract (4, 6). The results of a review of patients treated worldwide with imipenem/cilastatin for a variety of bacterial infections indicate that its frequence of adverse reactions and tolerance by patients parallel those of currently used beta-lactam antibiotics (7). This antibiotic, the first representative of a new class of beta-lactam antibiotics, the carbapenems, has a wide range of activity against most clinically important gram-positive and gram-negative human pathogens (8, 9). The results of tests against more than 3,000 isolates from burn patients treated at this institute prior to this clinical trial showed imipenem/cilastatin sensitivity in more than 99 per cent. The results of an *in vitro* survey at another burn center showed a sensitivity in 97 per cent of tested burn isolates (10).

cont'd nxt pg

From the United States Army Institute of Surgical Research, Fort Sam Houston, San Antonio.

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defe

ients participated in these studies after giving their and informed voluntary consent. Investigators adhered to Army Regulation 70-25 and United States Army Medical and Research Development Command Regulation 70-25 on the use of volunteers in research.

Citations of commercial organizations and trade names in this report do not constitute an official Department of the Army endorsement or approval of the products or services of these organization.

Reprint requests: Library Branch, U. S. Army Institute of Surgical Research, Fort Sam Houston, San Antonio, Texas 78234.

Reprint from SURGERY, *Gynecology & Obstetrics*, July, 1987, Vol. 165, 25–28

METHODS AND MATERIALS

Twenty patients were entered into the study. At entry, each had an acute bacterial infection with organisms susceptible to imipenem/cilastatin *in vitro*. Infections were diagnosed using the previous described criteria of this institute (11). Inhalation injury was diagnosed by broncoscopy or ^{133}Xenon scans of the lungs, or both (12, 13). Microbiologic effects of treatment were evaluated with daily qualitative or quantitative cultures of the infected sites and antibiotic sensitivity testing (14).

The antibiotic was administered as monotherapy at a dose ranging from 1 to 4 grams per day, the highest doses being administered to those with the most severe infections. The clinical and bacteriologic course of each patient was observed and documented, with evaluations made for bacteriologic and clinical efficacy as well as for the safety and patient tolerance of the regimen. Laboratory data were obtained before, during and after therapy to identify hematologic, renal or hepatic dysfunction, or all three.

RESULTS

The characteristics of the study group are presented in Table I. There were 18 males and two females. The average age was 38 years and the average burn size was 52 per cent of the total body surface area. Inhalation injury was present in 14. Among these 20 severely burned patients, pulmonary infections occurred in 16. Inhalation injury was present in 12 of 16 patients with pulmonary infections. Other infections included two instances of infections of the urinary tract, one instance of burn wound infection and one of bacteremia. The duration of monotherapy with imipenem/cilastatin ranged from three to 19 days, the average duration of therapy being nine days. Clinical improvement or cure occurred in 13 patients. Improvement occurred in nine of those with pulmonary infections and in all four of those with the other infections. No improvement was noted in five. Clinical response was considered indeterminate in two patients. In these two patients, multisystem organ failure preceding the infection treated with imipenem/cilastatin complicated the clinical evaluation of response to the drug. All of the clinical failures occurred in patients with pulmonary infection. Toxicity and side effects were minimal, with a transient skin rash noted at the site of infusion in one patient and transient premature ventricular contractions lasting one day in another. No patient died while receiving the drug or as a consequence of a known failure of the drug. Ultimately, six patients died. Of these six, two deaths occurred in the clinical improved group, two in the clinical failure group and two occurred in two patients in whom the clinical response was classified as indeterminate. These deaths occurred at an average of 33 days after imipenem/cilastatin therapy was begun.

Assessment of the microbiologic effects of imipenem/cilastatin treatment revealed that the infecting organisms were eradicated in six patients and were reduced in number or suppressed in six. In eight, the infecting organisms developed resistance or persisted. Of the eight microbiologic failures, five were associated with clinical failure. Of the five clinical failures, four had infections caused by *Pseudomonas aeruginosa* and the fifth was an infection caused by *Haemophilus parainfluenzae*. Of the eight patients in whom resistance developed, seven had infections caused by *Pseudomonas aeruginosa*. In this study, the emergence of imipenem/cilastatin resistant *Pseudomonas aeruginosa* was universal and occurred at an average of 3.6 days after the drug was begun. Development of *in vitro* resistance, however, was not uniformly associated with clinical failure.

DISCUSSION

Imipenem/cilastatin appears to be an antimicrobial of low toxicity that is clinically effective in the treatment of infections in seriously burned patients. In this study, 80 per cent of the patients have burns of more than 30 per cent of the total body surface area, 70 per cent also had inhalation injury and seven patients were more than 40 years old. Modern topical therapy limits the occurrence of burn wound infection, but such immunosuppressed patients remain uniquely susceptible to other infections.

In the absence of a concurrent control group, statistical inference concerning the effects of imipenem/cilastatin upon mortality in this study is inappropriate. The observed mortality in this group of patients was entirely consistent with that expected on the basis of recent experience in infected patients having injuries of this severity, indicating that imipenem/cilastatin monotherapy was at least as effective as the frequently used multiple antibiotic therapeutic regimens (15, 16).

Imipenem/cilastatin was clinically effective in most infections in this population; therapeutic failures occurred only in patients with pulmonary infections. Infections caused by *Pseudomonas aeruginosa* responded less favorably and were associated with rapid development of *in vitro* resistance; similar occurrences have been noted in

Keywords: Pseudomonas aeruginosa; Haemophilus parainfluenzae; therapy; resistance (biology); reprints

patients with pseudomonas infections in other patient studies (17–19). Adverse reactions to the antibiotic have been infrequently observed in previous studies, and our experience reaffirms the safety of this antibiotic (20–23).

SUMMARY

The results of this study indicates that monotherapy with imipenem/cilastatin is effective and safe when used for the treatment of a wide variety of infections in patients with severe burn injury. The incidence (100 per cent of all patients with *Pseudomonas aeruginosa* infections in this study) and rapidity (average 3.6 days after initiation of therapy) of the development of *in vitro* resistance to imipenem/cilastatin, however, indicates that infections in burned patients caused by *Pseudomonas aeruginosa* should not be treated with imipenem/cilastatin as a single agent.

REFERENCES

1. Pruitt, B. A., Jr. The diagnosis and treatment of infection in the burn patient. Burns, 1984, 11: 79-91.
2. Idem. The burn patient. I. Initial care. Curr. Prob. Surg., 1979, 16: 1-60.
3. Idem. The burn patient. II. Later care and complications of thermal injury. Curr. Prob. Surg., 1979, 16: 1-95.
4. Birnbaum, J., Kahan, F. M., Kropp, H., and others. Carbapenems, a new class of beta-lactum antibiotics: discovery and development of imipenem/cilasatin. Am. J. Med., 1985, Suppl. 6a, 78: 3-21.
5. Neu, H. C. Clinical perspectives on imipenem. J. Antimicrob. Chemother., 1983, Suppl. D, 12: 149-153.
6. Norrby, S. R. Imipenem/cilastatin: rationale for a fixed combination. Rev. Infect. Dis., 1985, Suppl. 3, 7: 447-451.
7. Calandra, G. B., Brown, K. R., Grad, L. C., and others. Review of adverse experiences and tolerability in the first 2,516 patients treated with imipenem/cilastatin. Am. J. Med., 1985, Suppl. 6a, 78: 73-78.
8. Jones, R. N. Review of the *in vitro* spectrum of activity of imipenem. Am. J. Med., 1985, Suppl. 6a, 78: 22-32.
9. Kropp, H., Gerckens, L., Sundelof, J. G., and others. Antibacterial activity of imipenem: the first thienamycin antibiotic. Rev. Infect. Dis., 1985, Suppl. 3, 7: 384-410.
10. Hansbrough, J. F., Carroll, W. B., Zapata-Sirvent, R. L., and others. Identification and antibiotic susceptibility of bacterial isolates from burned patients. Burns, 1985, 11: 393-403.
11. Shirani, K. Z., McManus, A. T., Vaughan, G. M., and others. Effects of environment on infection in burn patients. Arch. Surg., 1986, 121: 31-36.
12. Herndon, D. N., Thompson, P. B., and Traber, D. L. Pulmonary injury in burned patients. Crit. Care Clin., 1985, 1: 79-96.
13. Pruitt, B. A., Jr., Erickson, D. R., and Morris, A. Progressive pulmonary insufficiency and other pulmonary complications of thermal injury. J. Trauma, 1975, 15: 369-379.
14. McManus, A. T., McManus, W. F., Mason, A. D., Jr., and others. Microbial colonization in a new intensive care burn unit. Arch. Surg., 1985, 120: 217-223.
15. Shirani, K. Z., Pruitt, B. A., Jr., and Mason, A. D., Jr. The influence of inhalation injury and pneumonia on burn mortality. Ann. Surg., in press.
16. Mason, D. A., Jr., McManus, A. T., and Pruitt, B. A., Jr. Association of burn mortality and bacteremia: a twenty-five year review. Arch. Surg., in press.
17. Brooks, R. G., McCabe, R. E., Vosti, K. L., and others. Open trial of imipenem/cilastatin for serious bacterial infections. Rev. Infect. Dis., 1985, Suppl. 3, 7: 496-505.
18. Heseltine, P. N. R., Yellin, A. E., Appleman, M. D., and others. Imipenem therapy for perforated and gangrenous appendicitis. Surg. Gynecol. Obstet., 1986, 162: 43-48.
19. Nielsen, D. M., Katz, J. R., AhLoy, R. D., and others. Imipenen/cilastatin therapy for serious bacterial infections. Rev. Infect. Dis., 1985, Suppl. 3, 7: 506-512.
20. Trumbore, D., Pontzer, R., Levison, M. E., and others. Multicenter study of the clinical efficacy of imipenem/cilastatin for treatment of serious infections. Rev. Infect. Dis., 1985, Suppl. 3, 7: 476-481.
21. Acar, J. F. Therapy for lower respiratory tract infections with imipenem/cilastatin: a review of worldwide experience. Rev. Infect. Dis., 1985, Suppl. 3, 7: 513-517.
22. Chiodini, P. L., Geddes, A. M., Smith, E. G., and others. Imipenem/cilastatin in the treatment of serious bacterial infections. Rev. Infect. Dis., 1985, Suppl. 3, 7: 490-495.
23. Kager, L., and Nord, C. E. Imipenem/cilastatin in the treatment of intraabdominal infections. Rev. Infect. Dis., 1985, Suppl. 3, 7: 518-521.

TABLE I.—CHARACTERISTICS OF PATIENTS ENTERED INTO IMIPENEM/CILASTATIN STUDY

Patient No., Age, yrs., Sex	*Burn size*[*]	*Inhalation injury*	*Type of infection*	*Organism*	*Dose, gm./day*	*Treatment days*	*Clinical effect*	*Microbiologic effect*	*Adverse reactions*
1 ..... 36 M	56.0	Positive	Bacteremia	Enterobacter cloacae	4	11	Cured	Eradicated	None
2 ..... 36 M	79.0	Positive	Broncho-pneumonia, bacteremia	Staphylococcus aureus	4	9	Improved	Reduced in number	None
3 ..... 20 M	81.0	Positive	Broncho-pneumonia, bacteremia	Pseudomonas aeruginosa, Staphylococcus aureus	2	6	Not improved	Developed resistance	None
4 ..... 29 M	82.0	Positive	Broncho-pneumonia	Pseudomonas aeruginosa	4	6	Indeterminate	Developed resistance	None
5 ..... 28 M	70.5	Positive	Broncho-pneumonia	Pseudomonas aeruginosa	3	5	Not improved	Developed resistance	None
6 ..... 24 F	29.0	Negative	Broncho-pneumonia	Haemophilus parainfluenzae	2	8	Cured	Eradicated	Premature ventricular contractions (slight) for one day
7 ..... 27 M	43.0	Positive	Broncho-pneumonia	Proteus vulgaris, Staphylococcus aureus	3	9	Improved	Reduced in number, eradicated	None
8 ..... 33 M	84.0	Positive	Broncho-pneumonia	Escherichia coli	2	15	None	Reduced in number	None
9 ..... 64 M	48.3	Positive	Broncho-pneumonia	Pseudomonas aeruginosa	3	6	Improved	Persisted	None
10 ..... 55 M	54.0	Positive	Broncho-pneumonia	Pseudomonas aeruginosa	2	8	Not improved	Developed resistance	None
11 ..... 41 M	44.0	Positive	Broncho-pneumonia	Staphylococcus aureus	3	8	Cured	Eradicated	None
12 ..... 57 M	25.0	Positive	Broncho-pneumonia	Pseudomonas aeruginosa	4	9	Improved	Developed resistance	None
13 ..... 61 M	41.0	Negative	Broncho-pneumonia	Enterobacter cloacae	4	10	Cured	Reduced in number	None
14 ..... 70 M	32.0	Negative	Broncho-pneumonia	Escherichia coli	4	11	Indeterminate	Eradicated	None
15 ..... 31 M	45.0	Positive	Tracheo-bronchitis	Streptococcus viridans, Nonhemolytic Streptococcus, not Group D	2	12	Improved	Reduced in number	Slight rash at infusion site
16 ..... 13 M	60.0	Negative	Tracheo-bronchitis	Haemophilus parainfluenzae	2	3	Not improved	Developed resistance	None
17 ..... 52 M	56.0	Positive	Tracheo-bronchitis	Serratia marcescens	3	7	Improved	Eradicated	None
18 ..... 31 F	23.5	Negative	Urinary tract	Pseudomonas aeruginosa, Enterobacter cloacae	2	9	Improved	Developed resistance	None
19 ..... 27 M	22.0	Negative	Urinary tract	Klebsiella pneumoniae	2	6	Cured	Suppressed	None
20 ..... 23 M	38.0	Positive	Wound	Enterobacter cloacae	3	19	Cured	Eradicated	None

[*]Per cent of total body surface area burned.